REMARKS

The Examiner has made the restriction Final. (Paper No. 20080916 at 2.) We do not agree with the Examiner's position, however, that the claims lack unity of invention. It is also noted that we do not acquiesce in the Examiner's assertions on page 2 of the Action regarding Wanner *et al.*, E.J. Biochem. 1998, 255 pp..271-128 ("Wanner"), which were made in connection with claims 2 and 3. We here maintain the remarks and arguments regarding Wanner that were presented in the Response to Restriction Requirement Under 35 U.S.C. § 121 and 372, filed June 19, 2008. And, we reserve the right to present these and/or additional arguments regarding Wanner and/or claims 2 and 3, in the present application and/or a continuing application thereof.

Claim 7 has been amended. Support for the amendments is found in the Specification at, for example, page 1, lines 9-18, page 4, lines 8-13; and original claim 1. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP § 608.01(o) and (l).

Claims 9-14 have been added. Support for claim 9 is found in the Specification, for example, at page 6, lines 6-8; and in original claim 7. (Id.) Support for claims 10, 11, and 12 is found in the Specification at, for example, page 2, lines 9-10 and lines 19-21, and page 4, lines 8-15. Support for claim 13 is found in the Specification at, for example, page 2, lines 4-5; Example 5 at Page 11, line 16 to page 12, line 22; and SEQ ID NO:2. Support for claim 14 is found in the Specification at, for example, page 3, lines 3-5, the Examples, and SEQ ID NO:2.

Objection

Claim 7 was objected to as depending from a non-elected claim 6. (Paper No. 20080916 at 3.)

As noted above, claim 7 has been amended to place the claim in independent form. Withdrawal of the objection is requested.

Indefiniteness Rejection

Claim 7 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. (Id.) In making the rejection, the Examiner asserted "the phrase 'e.g.' renders the claim indefinite...". (Id.)

Claim 7 has been amended to, *inter alia*, delete the phrase "e.g.". Withdrawal of the rejection is requested.

Enablement Rejection

Claim 7 was rejected under 35 U.S.C. § 112, first paragraph, for lack of an enabling disclosure. (Id. at 4.) While the Examiner acknowledged that "the specification [is] enabling for the method of production of levodione from ketoisophorone using enone reductase SEQ 10 NO: 2", the Examiner nevertheless asserted that the Specification "does not reasonably provide enablement for [a] method of production of levodione from ketoisophorone using any enone reductase comprising a molecular weight of about 61 kD having any structure and characteristics recited ... (cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH

4.5-8.5) from any source." (Id.) The Examiner concluded that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." (Id.)

The Examiner further asserted that "[p]redictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired enone reductase activity (convert ketoisophorone to levodione) requires knowledge and guidance regarding [which] specific amino acid residue(s) in the protein's amino acid sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and detailed knowledge of the protein's structure, and the ways in which the protein's structure relates to its function." (Id. at 6.) In addition, the Examiner asserted that "[t]he positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired enone reductase (convert ketoisophorone to levodione) activity are limited in any protein and the result of such modifications is highly unpredictable." (Id.)

Furthermore, the Examiner asserted that "[t]he scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enone reductase with variable structures broadly encompassed by the claim. The specification discloses one working example of such enone reductase comprising SEQ ID NO: 2 that [was] isolated from *Candida kefyr.* However, the specification fails to disclose any specific guidance for altering the amino acid sequence of any enone reductase or enone reductase of SEQ ID NO: 2 with

expectation that the polypeptide will still have the same activity...". (Id. at 7-8) (underline in original.)

The Examiner concluded that "it would require undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention." (Id. at 8.)

Initially, we note that it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). To carry this burden, the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention. *Id.* at 370.

The Examiner has the burden to set forth a *prima facie* case by establishing a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982); *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

Although not explicitly set forth in the statute, enablement may be found where some experimentation (even a considerable amount) is required, so long as the experimentation is not "undue." *Ex parte Forman*, 230 USPQ 546, 547 (BPAI 1986); *see also In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (J. Miller concurring) (CCPA 1977); and *In re Rainer*, 347 F.2d 574, 577, 146 USPQ 218, 220-221 (CCPA 1965). The Federal Circuit, adopting the analysis set forth in *Forman*, has enumerated several factors which may be considered in determining whether claims require that one skilled in the art perform undue experimentation in order to practice the claimed subject

matter: breadth of the claims; predictability or unpredictability of the art; relative skill of those in the art; state of the prior art; nature of the invention; working examples; amount of guidance; and quantity of experimentation necessary. *Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. These factors are merely illustrative, not mandatory; they provide a general framework for analysis. *Enzo Biochem v. Calgene Inc.*, 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

In fact, enablement may still be present when an application contains no working examples or when prophetic examples are used. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984) ("Use of prophetic examples ... does not automatically make a patent non-enabling.") and *Strahilevitz*, 668 F.2d at 1232, 212 USPQ at 563 ("Nevertheless, as acknowledged by the board, examples are not required to satisfy section 112, first paragraph.").

To further prosecution in the present application, claim 7 has been amended to recite: "[a] process for the production of levodione, which comprises contacting ketoisophorone with an enzyme derived from *Candida* or *Zygosaccharomyces* which has enone reductase activity, wherein the enzyme is characterized by the following physico-chemical properties:

(a) molecular mass: 61,300±5,000 Da

(estimated using gel filtration, consisting of one subunit);

(b) co-factor: NADPH and NADH;

(c) substrate specificity: active on α,β-unsaturated ketones;

(d) optimum temperature: 55-60° C at pH 7.4; and

(e) optimum pH: pH 4.5-8.5,

at pH values in the range of from 4.5 to 8.5 and at a temperature in the range of from 10 to 60° C. for 5 minutes to 72 hours."

We respectfully submit that the Specification is sufficiently enabling for the claimed process as amended for the production of levodione, which uses an enzyme having the recited physico-chemical properties and which is "derived from *Candida* or *Zygosaccharomyces* [and] which has enone reductase activity". The Specification discloses, for example, obtaining an isolated DNA sequence encoding an active enone reductase which is derived from *Candida* or *Zygosaccharomyces*, and expressing the DNA sequence. The Specification discloses:

> The primers used for cloning of the enone reductase gene by PCR may be based on the amino acid sequence of the peptide fragments of the purified enone reductase from the genera including, but not limited to, *Candida* and *Zygosaccharomyces*, and in the most preferred embodiment, from *C. kefyr* (*C. macedoniensis*) IFO 0960. A DNA fragment (a partial DNA sequence) of enone reductase is generated by PCR amplification with the primers and the template of, e.g., *C. kefyr* chromosomal DNA. The amplified DNA fragment can be used as the probe to clone a genomic fragment coding for the whole enone reductase. (Page 4, lines 11-16.)

We also refer the Examiner to Examples 1-5 from Page 7, line 23 to Page 12, line 22, which disclose the use of partial amino acid sequences of enone reductase

of *C. kefyr* IFO 0960 and PCR procedures to obtain and express the enone reductase gene of *C. kefyr*, as well as production of levodione in the presence of the enzyme. The Specification thus provides guidance and direction to one skilled in the art as to how the enzyme may be obtained, thus enabling the full scope of claim 7 as amended.

We also refer the Examiner to U.S. Patent No. 7,202,068 ("the '068 patent"), which the Examiner has cited as the basis of a double patenting rejection. The '068 patent discloses that "[t]he microorganisms used ... are selected from yeast, including but not limited to microorganisms belonging to the genus *Candida* or *Zygosaccharomyces*, which are capable of producing enone reductase as defined hereinbefore." (Column 1, lines 49-53.) One skilled in the art would thus understand that an enzyme derived from *Candida* or *Zygosaccharomyces* can be obtained which has enone reductase activity.

It is respectfully submitted that the Specification discloses to one skilled in the art how to make and use the full scope of the claimed process without undue experimentation. Reconsideration and withdrawal of the rejection are requested.

Anticipation or in the Alternative, Obviousness Rejection

Claim 7 was rejected under USC § 102(b) as anticipated by or in the alternative, under 35 USC § 103 as obvious over Vaz et al., Biochem. 1995, 34, 4246-4256 ("Vaz").

Vaz disclose the role of old yellow enzyme (OYE) in the aromatization of cyclic enones and the mechanism of a novel dismutation reaction. (Title.) Vaz also

disclose that OYE was isolated from Brewer's Bottom Yeast. (Page 4247, left column, lines 1-3 under "Materials and Methods".)

In making the rejection, the Examiner asserted that Vaz "teach the use of old yellow enzyme (OYE1, an enone reductase that react[s] on alpha, beta-unsaturated ketone using NADPH and NADH cofactor) for the reduction of [the] olefinic bond and teach the conversion of ketoisophorone to levodione (Table 1 page 4252) at pH 7 and temperature 25° C and also teach the expression of ***OYE from S. cerevisiae*** in *E. coli.*" (Id. at 10) (emphasis added.) The Examiner further asserted:

> The same old yellow enzyme used by Vaz et al. is characterized by Stott et al. (JBC 1993, 268, 6097-6106 from IDS) showing [the] following characteristics: mwt of 47,000 by SDS gel electrophoresis, comprises ~400 amino acid residues and an amino acid sequence having 72% identical [sic] to applicants' enone reductase of SEQ ID NO: 2. A molecular weight of about 61 kD on gel filtration that taught by applicants [sic] enone reductase is an apparent mwt of fully formed and active enzyme. Molecular weight on gel filtration depends on the shape of the molecule as well as the degree of aggregation of the protein and is an approximate molecular weight. Applicants enone reductase shows Mwt of 45000 on SDS gel electrophoresis as a denatured protein (page 12 of the specification) and comprises [~]400 amino acid residues of SEQ ID NO: 2. Since the old yellow enzyme used by Vaz et al., which shows mwt of 47,000 by SDS gel electrophoresis, comprises ~400 amino acid residues and which is 72% identical to applicants' enone reductase of SEQ ID NO: 2, Vaz et al. anticipate applicants invention of claim 7. (Id. at 10-11.)

In addition, the Examiner asserted that the rejection is "being made under 35 USC 102(b) and 35 USC 103 because the examiner cannot distinguish the claimed method from that described by Stott et al." (Id. at 11.) The Examiner further asserted that "Applicants have the burden of distinguishing their claimed invention from that

taught in the prior art by providing evidence that show[s] the claimed method is different from that taught in the prior art. (Id.) The Examiner added that this may be shown by distinguishing "the enone reductase of the prior art and that of the instant application". (Id.)

As noted above, claim 7 has been amended to, *inter alia*, recite "an enzyme **derived from *Candida* or *Zygosaccharomyces*** which has enone reductase activity".

With respect to the rejection under § 102, we note that anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.* 221 USPQ 481, 485 (Fed. Cir 1984).

It is well settled the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

With respect to the § 103 rejection, we note that when patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and modify the document(s) relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727,

1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to modify document(s) must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion test "***must be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added). *See also Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 USC § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

Here, what the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Vaz in the manner proposed by the Examiner to arrive at the claimed process. As is well settled, an Examiner cannot establish obviousness by locating documents which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. June 28, 2007) (citing *KSR*) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Beyond looking at the references to determine if any of them suggests doing what the inventors have done, one must also consider if the art provides the required expectation of succeeding in that endeavor. See *In re Dow Chem. Co. v. American Cyanamid Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) "Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." *In re Clinton*, 188 USPQ 365, 367 (CCPA 1976). Furthermore, the U.S. Patent and Trademark Office Examination Guidelines at page 57527 provide the following guidance to Examiners: "In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge". However, no such motivation or expectation of success can be found in the cited document.

Vaz discloses that the OYE enzyme is isolated from Brewer's Bottom Yeast. (Page 4247, left column, lines 1-3 under "Materials and Methods".) The Examiner has asserted that OYE as disclosed in Vaz is from *S. cerevisiae*. (Paper No. 20080916 at 10.) Vaz, however, does not disclose an enzyme derived from *Candida* or *Zygosaccharomyces* which has enone reductase activity, as recited in amended claim 7. Because Vaz does not disclose each and every element of amended claim 7, anticipation cannot lie.

Moreover, the rejection does not identify anywhere in Vaz a teaching, suggestion, or motivation to achieve a process for the production of levodione using an enzyme derived from *Candida* or *Zygosaccharomyces* which has enone reductase activity. Nor has the Examiner provided any indication of motivation for one skilled in

the art to use the recited enzyme in the claimed process. The Examiner has instead acknowledged that "there was a high level of unpredictability [involved in obtaining an enzyme that] will maintain the ... desired biological activity." (Id. at 7.) In view of the foregoing, is submitted that one skilled in the art would not have had motivation to achieve and would not have expected success in the claimed process using the recited enzyme of amended claim 7.

It is respectfully submitted that Vaz neither anticipates nor renders obvious the claimed process. Reconsideration and withdrawal of the rejection are requested.

Double Patenting Rejection

Claim 7 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of U.S. Patent 7,202,068 ("the '068 patent"). (Id. at 12.) In making the rejection, the Examiner asserted that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other." (Id.)

Initially, it is noted that claim 7 has been amended as indicated above.

Upon indication of allowability, if this rejection is maintained, we will consider whether the filing of a Terminal Disclaimer is appropriate. In doing so, we note that it is appropriate to defer the filing of a Terminal Disclaimer until it is determined whether or not allowable claims would require it. See MPEP § 1490 VII(A) (8th Ed. Rev. 7, July 2008, p. 1400-118).

In view of all the foregoing, entry of the amendments and withdrawal of all outstanding objections and rejections is respectfully requested. It is submitted that the application is in condition for allowance. Issuance of a Notice of Allowance is respectfully requested.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 13, 2009.

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Respectfully submitted,

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